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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,553	NORMANT ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/821,811.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 24 December 2003 as a continuation of application 09/821,811, filed 30 March 2001. The Amendment filed 24 October 2003 has been entered in part. Specifically, the claim amendments are entered. Claims 1-47 were originally filed. Claims 1-47 were canceled and claims 48-87 were added in the 24 October amendment. The amendments to the specification have not been entered because they do not contain markings to show the changes made relative to the specification as filed. The amendment of the specification at page 1, line 1, to include the priority claim is also entered. The amendments to the specification at page 22, lines 11-13, and page 23, lines 1-6, are not entered because they do not include markings to show changes made relative to the original paragraph in accordance with the requirements of Rule 1.121. Applicant should resubmit the amendments with proper markings to show the changes made.

Claims 48-87 are pending and under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/821,811, filed on 30 March 2001.

Applicant is urged to update the priority claim in the first line of the specification to include the current status of the 09/821,811 application, which is now US Patent No. 6,696,267.

Claim Objections

Claims 55 and 56 are objected to because of the following informalities: "SEQ ID Nº" should be SEQ ID NO.

Claim 71 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recite that the method of claim 48 is used for screening a compound that modulates the Icrac-mediated calcium inflow but fails to provide any additional method steps that would distinguish the method of the dependent claims from the method of claim 1. Claim 1 is not further limited by the claim because the limitations recited in the dependent claims pertain only to the properties of the compounds that might be discovered or analyzed using the method of claim 1 and not to the process that is the claimed invention.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 80-87 are rejected under 35 U.S.C. 101 because the claimed invention is directed to nonstatutory subject matter. The claims are directed to cells containing a reporter construct comprising a reporter gene under the control of a NFAT-inducible promoter. The discussion of the reporter construct in the first full paragraph on page 9 of the specification does not indicate that the construct must be exogenous to the cell and in the second full paragraph on page 9 states,

"[t]he reporter gene can be any nucleic acid encoding a product whose presence in a cell can be determined". In view of the disclosure, the reporter construct can be construed as broadly reading on the NFAT gene as it occurs naturally (*i.e.*, the presence of NFAT in a cell can be determined). Therefore, the cells of the claims read on any naturally occurring cell that comprises an NFAT gene. Amending the claim to recite that the cells are recombinant as contemplated at page 9, lines 14-16, would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48 and 57 are indefinite in reciting that the calcium channel activator causes "selective depletion of intracellular calcium stores". The metes and bounds of the limitation are unclear because there is nothing in the claims or in the specification to indicate in what way the depletion of intracellular calcium stores is selective. For example, is the depletion selective for certain intracellular calcium stores and not others? If so, which calcium stores are selected and which are not? Without some limiting definition or explicit statement in the claims as to how depletion of intracellular calcium stores is selective, the skilled artisan would not be able to ascertain the metes and bounds of a calcium channel activator that causes selective depletion of

intracellular calcium stores. Therefore, the metes and bounds of the claims as a whole are indefinite.

Furthermore, claim 48 is drawn to a method comprising a selective calcium channel activator while the specification provides a definition only for a selective Icrac activator. It unclear whether the applicant intends that the limitation "selective calcium channel activator" encompass only those activators that are selective for the Icrac channel or if the limitation includes activators that are selective for other calcium channels. Although the preamble of the claim indicates that the intended use of the method is to screen for compounds that modulate Icrac activity, claim 49 further limits the calcium channel activator to an Icrac activator, suggesting that the activator of claim 48 comprises a broader scope than the preamble and specification would suggest. Additionally, claim 68 refers to "the Icrac activator" of claim 48, which for the reasons provided above does not have a clear antecedent basis. Therefore the metes and bounds of the claims are unclear.

Claims 49-56 and 58-79 are indefinite insofar as they depend from claims 48 and 57.

Claim 58 is additionally indefinite in reciting "the substrate of β-lactamase". There is no antecedent basis for the limitation in the claims and there are a variety of known substrates for β-lactamase (see, *e.g.*, EP 0 982 398 A1; made of record in the IDS filed 24 October 2003). Therefore, it is unclear what is being referred to as "the substrate of β-lactamase". Amending the claim to use the indefinite article (*i.e.*, "a substrate of β-lactamase") would be remedial.

Claims 65 and 66 are further indefinite in reciting, "at least 10 [or 50] compounds are contacted in parallel" without specifying what the compounds are contacted with. It would be

remedial to amend the claims to explicitly state that the compounds are contacted in parallel with the cell population as recited in claim 64.

Claim 76 is indefinite in reciting that the cells are "murine or rat". A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the limitation murine broadly encompasses both mice and rats and the claim also recites rats, which is the narrower statement of the range/limitation.

Claims 77 and 79 are additionally indefinite in reciting "said population comprises at least 80% of cells expressing the Icrac channel". The phrase literally reads as if the population comprises 80% of some other population of cells that expresses the Icrac channel, which does not make sense in the absence of a definition of the other population. It would seem that Applicant's intention is that 80% of the cells of said population express the Icrac channel and amending the claims accordingly would be remedial. The following language is suggested: The

method of claim 75 (or 78), wherein at least 80% of cells of said population express the Icrac channel.

Claim 80 is further indefinite in being directed to a method of using a cell as defined in claim 1. As claim 1 has been canceled the defining characteristics of the cell are unclear. Furthermore, claim 80 is indefinite in reciting that the kit comprises "a substrate" without indicating the properties of the substrate. The metes and bounds of the limitation are indefinite because the word "substrate" can have a variety of meanings and it is unclear which is intended. For example the "substrate" might be a substrate for the reporter gene or the substrate might be a substrate upon which the cells of the kit are plated. As it is unclear from the disclosure or the claims which meaning is intended, the metes and bounds of the limitation are unclear.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would be obvious over, the reference claim(s). The MPEP states, at §804,

> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. *In re Boylan*, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first " determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 103, since only the disclosure of the invention claimed in the patent may be examined."

Claims 48-79 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,696,267. Although the conflicting claims are not identical, they are not patentably distinct from each other.

First, the instant claims 48-54, 57, 58 and 69-71, like claims 1-17 of the '267 patent are directed to a method for screening compounds that modulate Icrac activity comprising contacting a test compound and a selective calcium channel activator with a population of calcium channel expressing cells, said cells further containing a reporter gene under the control of a NFAT-inducible promoter and determining the activity of the test compound on the channel by measuring the reporter gene expression in the cells. The instant claims are generic to all that is recited in the claims of the '267 patent except for the limitation that the selective calcium

channel activator causes selective depletion of intracellular calcium stores. However, in the sixth full paragraph in column 7 the specification teaches that a preferred Icrac activator is thapsigargin, which is a selective calcium channel activator that causes selective depletion of intracellular calcium stores. Therefore, practicing the method claimed in the '267 application with a selective calcium channel activator causes selective depletion of intracellular calcium stores would have been obvious to one of ordinary skill in the art and one would have been motivated to do so because the application identifies such a calcium channel activator as a preferred embodiment.

Likewise, claims 55 and 56, which limit the NFAT-inducible promoter to comprising multiple copies of the nucleotide sequence set forth as SEQ ID NO: 1, would be obvious because the limitation is identified as a preferred embodiment in the paragraph bridging columns 5-6; claims 59 and 60, which limit the substrate used in the method to being a ratiometric substrate and CCF2-AM, would be obvious because ratiometric substrates and CCF2-AM are identified as preferred embodiments in the fifth paragraph in column 9; claims 61 and 72-79, which limit the cell type used in the assay to one of various types of blood cell, would be obvious because the specification identifies the recited cell types as preferred embodiments in the paragraph bridging columns 4-5; claim 63, which limits the method to contacting the cells with the test compound and Icrac activator simultaneously, would have been obvious in view of the teaching in the third full paragraph in column 7 that, "[i]n a typical embodiment, each compound and activator is contacted simultaneously with the cells"; and claims 64-68, which limit the method to contacting with multiple test compounds in parallel, would have been obvious in view of the teaching in the

fifth full paragraph in column 6 that it is most preferable that at least 50 compounds are contacted in parallel.

In view of the forgoing, the skilled artisan would conclude that the claims of the instant application are obvious variants of the claims issued in the '267 patent. Therefore, the claims are properly rejected under the judicially created doctrine of nonstatutory double patenting.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-52, 54, 55, 57, 61-64, 67, 68, 70-73, 75-77, 80-82, 84 and 85 are rejected under 35 U.S.C. 102(b) as being anticipated by Kerschbaum et al. (1997) *J. Immunol.* 159:1628-1638.

Claim 48 is drawn to a method for screening compounds that modulate Icrac activity comprising: a. contacting a test compound and selective calcium channel activator that causes selective depletion of intracellular calcium stores with a population of calcium channel expressing cells, said cells comprising a reporter gene under the control of an NFAT-inducible promoter; and b. determining the activity of the test compound on a calcium release-activated channel by measuring reporter gene expression. Claim 57 is drawn to a method for screening compounds that modulate Icrac activity comprising: (a) contacting a test compound and selective Icrac activator that causes selective depletion of intracellular calcium stores with a population of

Icrac expressing cells, said cells containing a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; (b) contacting the cells of (a) with a substrate of the reporter gene; and (c) determining the activity of the test compound on the channel by assessing the hydrolysis of the substrate.

Kerschbaum teaches a method for screening compounds that modulate Icrac activity comprising: (a) contacting a test compound and selective Icrac activator (*i.e.*, thapsigargin, which causes selective depletion of intracellular calcium stores) with a population of Icrac expressing cells, which further comprise a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; (b) contacting the cells of (a) with a substrate of the reporter gene; and (c) determining the activity of the test compound on the channel by assessing the hydrolysis of the substrate (see especially page 1633, column 2, third full paragraph through page 1635 column 1, first paragraph; and Table III). The method taught by Kerschbaum is the same as the method of the instant independent claims.

Claim 49 limits the calcium channel activator and cells of claim 48 to an Icrac activator and Icrac expressing cells; claim 50 limits the method of claim 49 to contacting cells with the Icrac activator in the absence of a Protein Kinase C activator; claim 51 limits the Icrac activator of claim 49 to a product or treatment that selectively depletes intracellular calcium stores; and claim 52 limits the Icrac activator of claim 51 to thapsigargin. As described above, Kerschbaum teaches contacting Icrac expressing cells (see especially Figure 7) with the selective Icrac activator thapsigargin, which selectively depletes intracellular calcium stores, in the absence of a Protein Kinase C activator (see especially Table III). The cells, Icrac activator and method of

contacting the cells taught by Kerschbaum are the same as those taught by the instant application.

Claim 54 limits the NFAT-inducible promoter of claim 48 to a transcriptional promoter comprising an NFAT-responsive region; and claim 55 limits the NFAT-inducible promoter of claim 54 to a promoter comprising one or several copies of the nucleotide sequence of SEQ ID NO: 1. Kerschbaum teaches a construct comprising an NFAT-inducible promoter comprising the NFAT-responsive region of the human IL-2 promoter consisting of nucleotides –285 to –256 of the IL-2 gene (see Kerschbaum citation 10, *Proc Natl. Acad. Sci. U.S.A.* (1991) 88:3972-3976). SEQ ID NO: 1 of the instant application is 100% identical to nucleotides –283 to –254 of the human IL-2 gene, therefore the promoter taught by Kerschbaum is the same as the promoter taught in the instant application.

Claims 63 and 64 limit the method of claim 48 to contacting at least two test compounds simultaneously and in parallel with the cell population; claim 67 limits claim 48 to a method in which step a) is performed in a multi-well plate; and claim 68 limits the time between steps a) and b) of claim 48 to between 2 and 6 hours. Kerschbaum teaches a contacting step comprising contacting two test compounds in parallel (see especially Table III, CTX + TEA) with cells in a multi-well plate for 4 hours (see especially page 1629, column 2, first full paragraph). The contacting step taught by Kerschbaum is the same as the step taught in the instant application.

Claim 70 limits the method of claim 48 to selecting a test compound that reduces reporter gene activity and claim 71 limits the method of claim 48 to a method used for screening a compound that modulates Icrac-mediated calcium flow. Kerschbaum teaches a method according to claim 48 wherein the test compound reduces reporter gene activity (see especially Table III,

CTX) and to select a compound that modulates Icrac-mediated calcium flow. The method of Kerschbaum is therefore the same as the method of the instant application.

Claim 80 is drawn to a kit comprising a cell population as defined in claim 48, a support, and a substrate. As described above, Kerschbaum teaches each of the limitations of the kit.

Claim 61 limits the cells of claim 48 to a culture of blood cells selected from lymphocytes, mast cells, or dendritic cells; claim 62 limits the population of cells of claim 48 to between 10^3 and 10^6 cells. Claims 72 and 73 are drawn to the method of claim 48 wherein the cells are blood cells or lymphocytes containing a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; claim 75 limits the cells used in the method of claim 48 to rodent immune cells comprising a reporter construct comprising a reporter gene under the control of a NFAT-inducible promoter; claim 76 limits the population of claim 75 to murine or rat immune cells; and claim 77 limits the cell population of claim 75 to comprising at least 80% cells expressing Icrac. Claims 81 and 82 are drawn to a blood cell for use in the methods of claims 48 and 57 respectively wherein the cell contains a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; claims 82 is drawn to a lymphocyte for use in the methods of claim 48 wherein the cell contains a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; claim 84 is drawn to a population of rodent immune cells for use in the method of claim 48 wherein the cell contains a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter; and claim 85 limits the cell population of claim 41 to comprising at least 80% cells expressing Icrac. Kerschbaum teaches a method comprising assaying a culture of 5 X 10^4 cells of the murine-derived lymphocyte line B3Z containing a reporter construct comprising a reporter

gene under the control of an NFAT-inducible promoter (see especially page 1629, column 2, first full paragraph). The cells taught by Kerschbaum are the same as those taught in the instant application.

Because the methods, cells, Icrac activator, NFAT-responsive promoter, and kit taught by Kerschbaum are the same as those taught in the instant application, the limitations of the claims are met by Kerschbaum.

Claims 80-82, 86 and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Zlokarnik (1998) *Science* 279:84-88.

The limitations of claims 80-82 are recited above. Claim 86 is drawn to a population of human immune cells for use in the method according to claim 1 wherein the cell contains a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter and claim 87is directed to the population of claim 86 wherein at least 80% of cells express the Icrac channel. Zlokarnik teaches each of the limitations of the kit of claim 80 and a human-derived lymphocyte line (*i.e.*, Jurkat cells) containing a reporter construct comprising a reporter gene under the control of an NFAT-inducible promoter (see especially Figure 3 and the caption thereto). Absent evidence to the contrary, the cell line would comprise at least 80% of cells expressing an Icrac channel. The kit and cells taught by Zlokarnik is the same as those taught in the instant application, therefore the limitations of the claims are met by Zlokarnik.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-62, 64, 67, 68, 71, 78 and 79, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerschbaum in view of Zlokarnik.

The limitations of claims 48-52, 54, 55, 57, 61, 62, 64, 67, 68 and 71 are recited above. Claim 53 is drawn to the method of claim 48 wherein the reporter gene is a β-lactamase gene; claim 56 limits the promoter of claim 55 to a promoter comprising between 2 and 8 copies of the nucleotide sequence of SEQ ID NO: 1; claim 58 limits the reporter gene of claim 57 to β-lactamase under the control of an NFAT-inducible promoter and the substrate of claim 57 to the substrate of β-lactamase; claim 59 limits the substrate of claim 57 to a ratiometric substrate; claim 60 further limits the substrate of claim 59 to CCF2-AM; claims 78 and 79 limit the cells used in the method of claim 48 to a population of human immune cells expressing a reporter gene under the control of a NFAT-inducible promoter, wherein said population comprises at least 80% of cells expressing the Icrac channel. Kerschbaum, as described above, teaches all of the limitations of the claims except for a promoter comprising between 2 and 8 copies of SEQ ID NO:1, a β-lactamase reporter gene, a ratiometric substrate for β-lactamase and human immune cells. As described above, Zlokarnik teaches a method of using human immune cells comprising a β-lactamase reporter gene under the control of an NFAT-inducible promoter comprising a tandem trimer of the IL-2 promoter NFAT binding site. Zlokarnik also teaches detection β-

lactamase reporter gene expression using the ratiometric β-lactamase CCF2-AM. It would have been obvious to one of ordinary skill in the relevant art at the time the invention was made to modify the methods of Kerschbaum to include the reporter gene construct and substrate of Zlokarnik. Motivation to combine these teachings comes from Zlokarnik who teaches several advantages of the β-lactamase/ CCF2-AM reporter system including the ability to load cells with the reporter substrate without permeabilizing the cells, and the advantages of ratiometric detection as compared with simple fluorescence detection (see especially page 85, column 1). One would have a reasonable expectation of success in combining these teachings in light of the very similar expression systems used in Kerschbaum and Zlokarnik, and in light of the fact that the cell line of Zlokarnik can be used in the methods of Kerschbaum without modification.

Claims 48 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerschbaum in view of Akong (1993) WO 93/13423.

The limitations of claims 48 and 64 are recited above. Claims 65 and 66 are drawn to the method of claim 64 wherein at least 10 or at least 50 compounds, respectively, are contacted in parallel. As discussed above, Kerschbaum teaches all of the limitations of the claims except contacting the cells with 50 or more compounds in parallel. Akong teaches a method of screening compounds for biological activity comprising adding "one or more compounds" in parallel, which encompasses the 50 or more compounds of the instant application (see especially page 47, second full paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Kerschbaum to include the addition of multiple compounds in parallel taught by Akong. One would be motivated to combine these

teachings in order to increase the throughput of the screening assay, which is known in the art to be desirable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

12/13/05

DANIEL M. SULLIVAN
PATENT EXAMINER